

Figure 1. Schematic drawing of *LRRK2* with predicted protein domains

(LRR – leucine rich repeat, Roc – Ras in complex proteins, COR – domain C-terminal of Roc, MAPKK – mitogen-activated protein kinase kinase, WD40 – WD40 repeats). The human *LRRK2* protein sequence in the region of the G2019S mutation is aligned with orthologs from rat (XP_235581), mouse (AAH34074), frog (AAH76853), and puffer fish (CAG05593). The chromatogram shows the 6055G>A transition (G2019S)

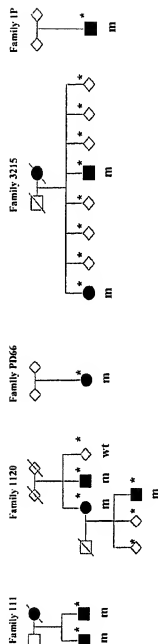


Figure 2. Pedigrees of families with *LRRK2* G2019S
□ and ○ denotes sexes, and 0 denotes that the sex is not given. A diagonal line across the symbol denotes that the person is dead, and thus that he/she has not been tested. Blackened symbols denote affected family members with parkinsonism. An asterisk denotes genotyped individual, with "m" for mutation carriers and "wt" for wild-type *LRRK2*. To protect confidentiality, the genotypes and genders of some unaffected individuals are not shown.

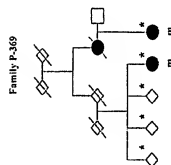
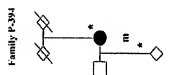
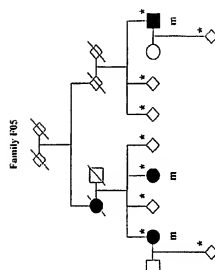
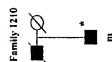
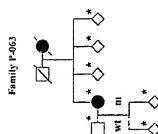
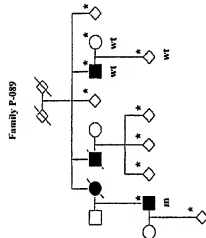
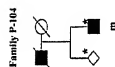
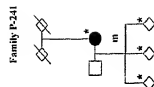


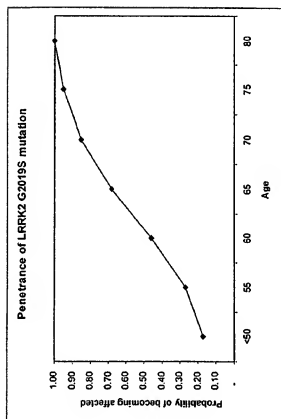
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Figure 3. Chromosome 12q12 STR markers on the disease haplotype (PARK8).

Marker	Family proband												Country of origin
	P-063	P-089	P-104	P-241	P-369	P-384	F05	1210	1120	111	3216	PD66	1P
D12S87	160	160	164	164	166	166	166	156/158	164	160	158	156/168	156/168
D12S1648	120	120	122	122	122	110	110	122/124	110	110	110	120/134	128/130
D12S2080	168	168	168	168	168	168	168	184/192	188	180	184	186/192	184/188
D12S2194	265	265	265	265	265	265	261	253/261	257	257	253	245/249	249/261
-31Kb	290	290	290	290	290	290	290	280/290	290	290	290	290/293	284/290
LRRK2_69Kb	223	223	223	223	223	223	223	210/223	223	223	223	215/215	211/219
LRRK2_129Kb	453	453	453	453	453	453	453	450/453	453	453	453	453/453	453/453
212Kb	132	132	132	132	132	132	132	130/132	132	132	132	132/138	132/134
243Kb	315	315	315	315	315	315	315	315/315	315	315	315	315/315	315/315
378Kb	168	168	168	168	168	168	168	168/168	168	168	168	168/168	168/168
D12S1048	214	214	214	214	214	214	214	214/223	214	214	214	211/214	211/228
D12S1301	112	116	120	120	118	118	116	108/116	100	120	118	100/116	100/100
D12S1701	95	97	91	91	95	95/97	97	95/101	92	91/95	95	97/101	91/97
	Norway												
	United States												
	Ireland												
	Poland												

Genotypes for probands from 13 families with *LRRK2* G2019S are shown; those shared are highlighted in grey.

Figure 4. Probability of becoming affected by parkinsonism, in *LRRK2*G2019S carriers, as a function of age.



LRRK2	DYGLAQ-----YCCRMGIKTSEGTGFPRAPE
LRRK1	DYGLSR-----QSFHEGALGVEGTGFGYQAPE
MATK	DFGLAK-----AERKGLDSSRLFPVKWTAPE
PDGFRA	DFGLARDIMHDSNYVSKGSTFLFVKWNAPE
MAP3K10	DFGLAR-----EWHKTRKSAAGTYAWNAPE
DAPK1	DFGN-----EFKNLFGCTEEFVAPE
BRAF	DFGLATVKSRWSSGSHQFEQLSGSILWNAPE

Figure 5. Aligned amino acid sequences of the activation loop of different human kinases.

In most kinases, the activation loop starts and ends with the conserved residues DFG and APE, respectively. In *LRRK2* and *LRRK1* phenylalanine is changed to tyrosine, an amino acid with a similar structure. (*LRRK2* – leucine-rich repeat kinase 2, *LRRK1* – leucine-rich repeat kinase 1, *MATK* – megakaryocyte-associated tyrosine kinase, *PDGFRA* – platelet-derived growth factor receptor alpha, *MAP3K10* – mitogen-activated protein kinase kinase kinase 10, *DAPK1* – death-associated protein kinase 1, *BRAF* – v-raf murine sarcoma viral oncogene homolog B1)